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**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

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| Appl. No. | : | 10/535,000 |
| Confirm No. | : | 1933 |
| Applicants | : | Masakazu HATANO |
| Filed | : | May 16, 2005 |
| For | : | THERAPEUTIC AGENT FOR GLAUCOMA COMPRISING Rho KINASE INHIBITOR AND β-BLOCKER |
| Art Unit | : | 1612 |
| Examiner | : | Gigi Georgiana HUANG |
| Docket No. | : | 05318/HG |
| Customer No. | : | 01933 |

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**PRE-APPEAL BRIEF CONFERENCE REQUEST**

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

S I R:

Review and withdrawal of the Rejection in the above-identified application is respectfully requested. No amendments are being filed with this request, and this request is being timely filed with a Notice of Appeal. The review and reversal of the Examiner are requested for the reasons set forth on the following five pages of explanation.

**Filed herewith: Notice of Appeal**

**Petition for Extension of Time**

**Claims 1-2, 4 and 13 are rejected as obvious over Azuma et al. (WO 00/09162).**

1. In response to applicants' position that Azuma et al. do not teach or suggest a combination of a Rho kinase inhibitor and another anti-glaucoma agent, the Examiner states that this is not accurate or persuasive. The Examiner points out that Azuma et al. teach Rho kinase inhibitors to be useful in combination with other compounds for glaucoma (see the June 21, 2010 Office Action, page 2, last six lines). However, the Examiner refers to many portions of Azuma et al. (i.e., column 2, lines 25 to 28; column 7, lines 1 to 58; column 8, lines 50 to 58; and column 9, lines 4 to 6), none of which suggest that Rho kinase inhibitors should be used with different effective agents, e.g., the β-blocker timolol. Nor is there a suggestion that such a combination would be effective. Rather, there is a teaching away from the use of timolol, as detailed below.

2. On page 3, lines 1 to 3 of the June 21, 2010 final rejection, the Examiner again refers to column 9, lines 4 to 6 of Azuma et al. as teaching a combination therapy. What Azuma et al. state is as follows:

> "In the present invention a compound having one kind of Rho kinase inhibitory activity can be used alone or, where necessary, several kinds of the compounds can be used."

3. This is not a teaching of a combination therapy that would support the Examiner's interpretation of the art. It is a

teaching that several kinds of Rho kinase inhibitors can be used. This is further comfirmed by the Background Art of Azuma et al. described below.

4. In the Background Art, Azuma et al. teach that the use of beta-adrenalin blockers is limited because of side effects thereof, such as dry eye and bradycardia, etc. (column 1, lines 39 to 48 of Azuma et al.). The Examiner states that, as is common with any medication, this description means that the beta-adrenalin blockers are not applied to patients with these symptoms (as one does not give sugar to a diabetic), but can be given to those without those particular conditions (see the June 21, 2010 Office Action, page 3, lines 3 to 15).

5. However, the Examiner's reasoning is against the common sense in the art. It is also out of context with the disclosure at column 1, lines 26 to 56 of Azuma et al., which lists other agents and why they should not be used (i.e., their very substantial and difficult side effects). A person of ordinary skill in the art understands that anti-glaucoma agents causing various adverse symptoms (e.g., beta-adrenalin blockers) possibly harm not only patients with these symptoms, but all patients (including patients without symptoms) and therefore should be avoided for use in glaucoma therapy. That is, at column 1 (above), Azuma et al. suggest that beta-adrenalin blockers and others are undesirable therapeutic agents for treating glaucoma. Adding them to the Rho kinase inhibitor would lead one to expect

the type of difficulties listed at column 1, lines 39 to 48 of Azuma et al. It is therefore respectfully submitted that Azuma et al. teach away from the presently claimed invention.

6. The Examiner's position that intended use of composition does not have patentable weight in a composition claim is a clear error (see the June 21, 2010 Office Action, page 4, lines 1 to 2). As the present invention is not known in the art, it is submitted that the intended use should be considered in any analysis of obviousness. This legal argument is detailed on page 13, line 3 to page 15, line 4 of the Amendment Under 37 CFR 1.111 filed March 23, 2010. Said legal argument includes a reference to and an excerpt from In re John B. Sullivan and Findlay E. Russell, 498 F.3d, 1345, 84 USPQ2d 1034 (Fed. Cir. 2006).

7. The inappropriateness of the Examiner's position with respect to intended use is especially notable here, where the intended use teaches away from the Examiner's obviousness rejection, as is detailed hereinabove at paragraphs 4 and 5. Also, if the composition is not for use in the eye, what is the use to render the composition obvious?

8. The Examiner points out that the present claims do not have any concentrations (see the June 21, 2010 Office Action, page 4, lines 5 to 7), but in applicants' present claim 1, there is a limitation relating to concentration (i.e., "pharmaceutically effective amount of"). That is, the comparative tests of record

show that several kinds of therapeutic agents for glaucoma comprising combinations of pharmaceutically effective amounts of (R)-(+)-N-(1H-pyrrolo[2,3-b]pyridine-4-yl)-4-(1-aminoethyl)benzamide (Y-39983) and timolol can yield synergism.

9. The Examiner points out that the amount of the IOP reduction at hour 2 in the July 21, 2009 HATANO DECLARATION is not synergistic, whereas the IOP reduction of combination group (5.5 mmHg) is more than the theoretical additive IOP reduction (4.9 mmHg) (see page 4, lines 8 to 21 of the June 21, 2010 Office Action). The Examiner does not allege a reason that IOP reduction at hour 2 is additive and not synergistic. Rather, the Examiner states on page 4, lines 8 to 12 of the June 21, 2010 Office Action that the arguments are based on future intended use (see discussion in 6 (above) regarding intended use). This is contrary to U.S. Patent Law, which requires only that the composition have unexpected properties related to its utility. See the discussion of In re Papesch, 315 F.2d 381,391, 37 USPQ 43 (CCPA 1963) in the excerpt of In re Sullivan in the March 23, 2010 Amendment Under 37 CFR 1.111(see 6 (above).

10. The Examiner points out that the comparative test is not reflective of the present claim because Y-399983 was given separately from the timolol, not together as in a single composition (page 4, last several lines of the June 21, 2010

Office Action). However, the interval between instillations of Y-39983 and timolol is a mere five minutes, and it is considered to be clear that the same result as the comparative test can be obtained when a single composition is used. Thus, the comparative test is reflective of applicants' present claims.

Respectfully submitted,

Holtz, Holtz, Goodman
& Chick PC
220 Fifth Avenue, 16th Fl.
New York, NY 10001-7708
Tel. Nos. (212) 319-4900
(212) 319-4551/Ext. 219
Fax No.: (212) 319-5101
E-Mail Address: RBARTHHHPATENT.COM
RSB/ddf

RICHARD S. BARTH
Reg. No. 28,180

Encs.: (1) NOTICE OF APPEAL

(2) PETITION FOR EXTENSION OF TIME